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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/876,187	LIPTON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 58-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 58-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed October 16, 2007 has been entered. The Notice of Non-Compliant Amendment issued October 5, 2007 is withdrawn in view of the submission of a complete claims listing. The amendment and remarks filed July 19, 2007 (hereinafter referred to as "the response") have been entered. Claims 1 and 59 have been amended.

Claims 1-20 and 58-79 remain pending in the instant application.

The rejection of Claims 1-20 and 58-79 under 35 U.S.C. 112, second paragraph, as being indefinite in their recitation of "protected neuronal cells," is withdrawn in view of the amendments to Claims 1 and 59 to recite "a cell population containing neuronal cells protected from apoptotic cell death."

The rejection of Claims 1, 18, 20, 59, 76, and 78 under 35 U.S.C. 102(b), as being anticipated by Mao et al. (1996, J. Biol. Chem. 271(24): 14371-14375), is withdrawn in view of Applicants' arguments at page 14 of the response.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for Claims 1-20 and 58-79 of this application, for the same reasons discussed hereinbelow as applied to the present application. Application serial no. 60/209,539 fails to provide an enabling disclosure for the invention now being claimed in Claims 1-20 and 58-79, for the reasons discussed herein below as a rejection under 35 U.S.C. 112, first paragraph, as applied to the instant application.

Thus, the earlier-filed application does not meet the requirements under 35 U.S.C. 119(e) for the benefit of obtaining priority to an earlier-filed application, as the earlier-filed application does not enable the full scope of the presently claimed invention.

At page 7 of the response, Applicants refer to their arguments below pertaining to the enablement rejection and assert that the specification provides sufficient description and guidance to enable the claimed methods. Accordingly, Applicants assert that priority to June 5, 2000 should be granted. Applicants' arguments regarding the enablement rejection are addressed in detail below and were not found persuasive to overcome the rejection. Accordingly, the earlier-filed application does not meet the requirements under 35 U.S.C. 119(e) for the benefit of obtaining priority to an earlier-filed application, as the earlier-filed application does not enable the full scope of the presently claimed invention, for the same reasons discussed hereinbelow.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 and 58-79 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action mailed 6/16/04, on pages 2-12 of the Office Action mailed 11/29/04, and on pages 2-12 of the Office Action mailed 8/12/05, and on pages 3-19 of the Office Action mailed 1/19/07, and for the reasons as discussed herein, because the specification, while being enabling for

a method of differentiating progenitor cells *in vitro*, comprising the steps of (a) contacting *in vitro* said progenitor cells with retinoic acid; and (b) introducing *in vitro* into said progenitor cells a nucleic acid molecule encoding an MEF2C polypeptide, wherein said progenitor cell is selected from the group

consisting of a P19 cell and a mouse embryonic stem cell, thereby differentiating said progenitor cells to produce a cell population containing neuronal cells protected from apoptotic cell death,

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

The following factors have been considered.

Nature of the invention and scope of the claims. The claims are directed to a method of differentiating progenitor cells, particularly embryonic stem cells and hematopoietic stem cells. The claims encompass *in vivo* and *in vitro* applications of the method. The claims cover a wide variety of different types of stem cells and progenitor cells that could be used as the starting material. The progenitor cell may be in culture or may be an endogenous cell residing *in vivo*. The specification asserts that the cell compositions developed from the claimed method are useful in therapeutic transplantation. Thus, the sole asserted utility for the claimed invention is to produce a therapeutic effect. The claims are broad in scope and cover the use of any differentiating agent in combination with any progenitor cell, as well as a wide variety of MEF2 polypeptides encoded by the nucleic acid. Consequently, the method covers the production of a very large variety of heterogeneous cell compositions that comprise protected neuronal cells.

Amount of direction or guidance presented and the presence or absence of working examples. The examples of the specification are limited to producing a cell composition from a mouse embryonal carcinoma cell line (P19 cells) transfected with an MEF2 nucleic acid molecule or mouse ES cell line (D3 cells) transfected with an MEF2 nucleic acid molecule. Cells expressing MEF2C exhibited a bipolar cell phenotype that expresses both neuronal (neurofilament) and myogenic (myosin heavy chain) markers (specification at page 68, paragraph 2). All experiments were in vitro assays. The specification does not provide examples of *in vivo* differentiation or *in vivo* transfection of progenitor cells. The specification teaches that the cell compositions produced from the claimed method can be used to treat a wide variety of neurodegenerative diseases, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease and other forms of dementia, multiple sclerosis, epilepsy, and pain (pages 1-3). With regard to the use of the cell compositions produced, i.e. for treatment of a neurodegenerative disease, the specification provides only general guidance rather than specific guidance. With regard to *in vivo* uses of the method to produce a treatment effect, the specification provides little to no guidance. The specification does not assert a utility for the *in vivo* application of the method in the absence of a treatment effect. The specification does not offer specific guidance as to how the cell compositions produced can be used therapeutically for any given disorder. No working examples demonstrate a therapeutic effect upon transplantation of the claimed composition. Methods of treating neurodegenerative disorders by cell therapy or *in vivo* gene therapy are in their infancy. Therefore, considerable guidance is needed.

State of the prior art and predictability of the art. The specification fails to provide an enabling disclosure for the therapeutic use of the cell compositions produced from the claimed method. Thus, the specification fails to teach how to use the claimed invention for the only asserted utility. At the time the invention was made, successful implementation of cell therapy and gene therapy protocols was not routinely achievable by those skilled in the art.

Rossi and Cattaneo (2002) acknowledge that "despite intense research activities and media attention, stem cell therapy for neurological disorders is still a distant goal" (abstract). The reference emphasizes the need for homogeneous populations of neural stem cells and the further need to understand the mechanisms required for "their proper integration into the injured brain" (abstract). The authors point out that "the functional integration of donor cells remains a highly demanding task that requires a profound understanding and control of the biological properties of both donor cells and the host environment" (page 401, column 2, paragraph 2, last sentence).

Cao et al. (2002) acknowledge the potential for the use of stem cells in therapeutic transplantation and for *in vivo* manipulation of endogenous precursors, but emphasize that "this at present is challenging and so far has been unsuccessful" (abstract and page 507, column 2, paragraph 2). The authors further point out that "[u]nderstanding mechanisms of NSC differentiation in the context of the injured CNS will be critical to achieving these therapeutic strategies" (abstract and page 507, column 2, paragraph 2). Given the unpredictability in the art of therapeutic transplantation, the development of therapeutic protocols requires substantial experimentation.

Mehler et al. (1999) disclose that many studies have suggested that the normal adult brain may lack the appropriate environmental signals to allow neural progenitors to realize their broad lineage potential. Specific neuropathologic conditions may alter the normal balance of regional environmental signals, for example by releasing proinflammatory and other modulatory cytokines. The presence of these inappropriate cellular cues may predispose residual neural populations to undergo apoptosis. The authors state that "[t]his suggests that it may be necessary to promote lineage commitment of progenitor cells *in vitro* prior to transplantation into a damaged brain" (p. 782, column 1, paragraph 1).

The specification fails to provide an enabling disclosure for the methods of making a cell population containing protected neuronal cells because the specification teaches that the only use for the compositions produced is for therapeutic transplantation, but methods of transplantation of neural tissue

or other cells into the CNS or PNS are not routinely successful and the specification does not offer adequate guidance to enable one skilled in the art to practice the claimed invention to derive a therapeutic benefit in a diseased animal. The specification teaches that the only use for the compositions produced from the claimed method is for transplantation to produce a therapeutic effect but the specification does not adequately teach how to use the cell compositions produced by the claimed method to produce such an effect. Jackowski et al. (1995) details the limitations and unpredictability associated with the transplantation of neural tissue. At page 311, column 1, paragraph 2, the reference discusses the barriers to successful transplantation of neural tissue, notably the presence of molecules that actively inhibit the regeneration of mammalian CNS and PNS axons. Grados-Munro et al. (2003) further disclose that axon outgrowth inhibition is a major barrier to axon regeneration in the CNS. Various myelin-associated inhibitors have been identified and their *in vivo* inhibitory effects have been characterized. The authors contemplate that a combination of approaches, including treatment to neutralize the inhibitory character of the CNS environment, may be required for CNS regenerative therapy (page 479). Other problems relating to appropriate environmental cues for axon guidance are also discussed. Filbin (2003) also discloses that inhibitors of axonal regeneration are present in the adult mammalian CNS and further discusses the inhibitory effect of glial scars which form after injury. Growth cone collapse is noted as the first event in inhibition of axonal growth and the response of neurons to inhibitors is discussed, including the current state of the art with regard to the intracellular inhibitory signalling pathway. Mehler et al. (1999) details the unpredictability and technical problems encountered in using progenitor cells for neural regeneration, particularly in the CNS. The authors state that "the reconstitution of more complex and widespread neural populations damaged by a variety of genetic or acquired neurological disorders such as stroke or traumatic injury will require access to a broader array of neural lineage species and a greater understanding of the developmental signals that sanction integration into the host environments. Many studies have suggested that the normal adult brain may lack the appropriate environmental signals to

allow neural progenitor species present in multiple mature CNS regions to realize their broad lineage potential" (page 781, column 2, paragraph 2). The instant specification does not offer specific guidance as to how the full scope of the compositions produced by the claimed method could be used therapeutically for the treatment of any disorder, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), AIDS dementia complex, Rett Syndrome, epilepsy, ischemia, spinal cord damage, hepatic encephalopathy, Tourette's syndrome, or drug addiction, as contemplated in the specification. These diseases involve ongoing pathological processes that affect the survival or function of endogenous neurons as well as transplanted neurons. Neither the specification nor the prior art provides evidence that the cell compositions produced by the claimed method will provide a therapeutic effect in these environments upon transplantation. Furthermore, neither the specification nor the prior art provides evidence that *in vivo* differentiation of progenitor cells residing *in vivo* can be used to provide a therapeutic effect in such disease environments. Moreover, Jackowski points out that membrane-associated or extracellular matrix-associated molecules that **inhibit** the successful regeneration of adult mammalian CNS and PNS axons are present in the CNS and PNS (page 311, column 1, paragraph 2).

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

In view of the quantity of experimentation necessary to determine appropriate parameters for using the resulting cell compositions to achieve a therapeutic outcome, and given the lack of applicable working examples directed to therapeutic transplantation, the limited guidance in the specification with regard to transplantation protocols and their applicability to pathologic conditions, the broad scope of the claims with regard to the wide variety of progenitor cells that may be used and the wide variety of cell

compositions that may be developed from the claimed method, and further given the unpredictability in the art of therapeutic transplantation, undue experimentation would have been required for one skilled in the art to practice the claimed methods to make useful cell compositions and use the claimed method in vivo to achieve a therapeutic effect.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of progenitor cell types that could be used, the unpredictability for achieving a therapeutic effect upon the transplantation of the resulting cell compositions, and the unpredictability for carrying out the claimed method *in vivo*, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a human patient for therapeutic benefit.

Even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification fails to provide an enabling disclosure for the genetic modification of human ES cells. The recent literature addresses the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. (2003) points out that there are significant differences between mouse and human ES cells and that "[h]igh, stable transfection efficiencies in human ES cells have been difficult to achieve, and, in particular, electroporation protocols established for mouse ES cells work poorly in human ES cells" (abstract). Thus, it is clear that the behavior of mouse ES cells is not predictive of human ES cells. In April 2001, Eiges et al. compared the efficiency of several different transfection protocols for human ES cells. The reference demonstrates use of the transfection protocol of ExGen 500 to transfect human ES cells. However, the instant specification does not provide specific guidance for transfecting human

ES cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. The teachings of Eiges et al. (2001) would not have been available to the skilled artisan as of the claimed priority date of this application which is June 5, 2000.

Regarding gene transfer into human HSCs, even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification contemplates that transfecting the ES cells with a nucleic acid encoding an MEF2 and contacting the cells with a differentiating agent will be sufficient to direct the cells to differentiate *in vivo* or *in vitro* into the appropriate cell type and functionally integrate into the tissue into which they are implanted. However, the state of the art for *in vivo* differentiation of ES cells is undeveloped. While much work has been done to develop techniques for the directed differentiation of ES cells *in vitro* to produce desired cell types, little is known about the behavior of these cells *in vivo* or how they will interact with the local environment when implanted into adult tissues. Jackowski (1995) details the limitations and unpredictability associated with the transplantation of neural tissue.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of stem or progenitor cell types that could be used, and the unpredictability for producing cells suitable for therapeutic transplantation, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention to produce useful cell compositions.

At pages 7-8 of the response, Applicants object to the teachings of Rossi and Cattaneo (2002) as not relevant to the claimed methods of producing protected neuronal cells because, Applicants allege, the issues that may exist for generating homogeneous populations of neural stem cells or the functional

integration of donor neural stem cells and their biological properties as discussed in Rossi and Cattaneo are not relevant to the claimed methods. On the contrary, given that the present claims cover the *in vivo* manipulation of any type of progenitor cell, including neural stem cells, with the asserted utility of providing a cell therapy, absent specific guidance on how to produce a therapeutic result, undue experimentation would have been required for a skilled artisan to enable the *in vivo* embodiments of the claim. While non-therapeutic *in vivo* gene transfer is relatively routine in the art, therapeutic protocols involving gene transfer and *in vivo* differentiation are not routine. There is no utility for non-therapeutic *in vivo* embodiments of the claimed method. The Rossi and Cattaneo reference aptly demonstrates the unpredictability in the field of cell therapy. As claimed, the method for producing neuronal cells protected from apoptotic cell death may be carried out *in vivo* or *in vitro* and the progenitor cells used as the starting material may be any type of progenitor cell, including neural stem cells. Thus, the reference is extremely relevant to the claimed invention. The claims recite the use of "progenitor cells" and "human stem cells." Both terms include neural stem cells. The specification does not provide a special definition for the term "progenitor cells," such that the terminology excludes neural stem cells. It is clear that the term "progenitor cells" includes all types of stem cells, including neural stem cells, hematopoietic stem cells, embryonic stem cells, embryonic carcinoma cells, and others. Accordingly, the specification must enable *in vivo* and *in vitro* embodiments over the full scope of progenitor cells covered by the claims.

At page 8 of the response, Applicants assert that Cao et al. (2002) describes the manipulation of endogenous neural precursors as challenging and unsuccessful. Applicants assert that the issues with respect to the manipulation of endogenous neural precursors in general are not relevant to the claimed methods reciting specific steps for differentiating cells *in vitro* or *in vivo*. On the contrary, the present claims cover the manipulation of endogenous neural precursors, as well as any other type of endogenous progenitor cell, and therefore the issues with respect to the manipulation of endogenous neural precursor

are clearly relevant. Cao et al. need not discuss stem cells in general to demonstrate the unpredictability in the art, particularly in methods where progenitor cells are to be used directly or indirectly for purposes of therapeutic transplantation. As Applicants acknowledge, the instant specification teaches that cells can be transplanted into a patient prior to, during or after differentiation of the progenitor cells into neuronal cells and that the neuronal environment can drive the cells into the desired cell type due to the presence of the appropriate environmental cues (page 58, line 29 to page 59, line 11). Applicants assert that Cao et al. "describes the manipulation of endogenous neural precursors as challenging and unsuccessful" (emphasis original) and that "[i]n contrast, the claimed methods are directed to differentiating progenitor cells to produce a cell population containing neuronal cells protected from apoptotic cell death by contacting the progenitor cells with a differentiating agent and introducing a nucleic acid encoding a MEF2 polypeptide or active fragment thereof." However, the presently claimed invention also is directed, in relevant part, to the *in vivo* manipulation of endogenous precursors. As noted in the rejection of record, the progenitor cell may be in culture or may be an endogenous cell residing *in vivo* (page 3, lines 1-2 of the Office Action mailed 8/12/05). Thus, the claims clearly cover contacting an endogenous neural stem cell, or any other endogenous progenitor cell, with a differentiating agent and introducing a nucleic acid encoding a MEF2 polypeptide into the endogenous neural stem cell, or other endogenous progenitor cell. The specification provides the explicit teaching that

> "a progenitor population in which the p38 MAP kinase/MEF2 pathway has been induced can be transplanted into a patient prior to, during or after differentiation of the progenitor cells into neuronal cells. In one embodiment, cells are transplanted prior to or during differentiation. Where cells are transplanted prior to differentiation, the neuronal environment can drive the cells into the desired neuronal cell type, rather than, for example, muscle cells due to the presence of the appropriate environmental cues. In view of the above, it is clear that differentiation can occur *in vitro* or *in vivo*, or can occur partially *in vitro* and partially *in vivo*." (page 58, line 29 to page 59, line 11)

As noted in the rejection of record, the claims encompass *in vivo* and *in vitro* applications of the method. The method steps can be carried out entirely *in vivo*, entirely *in vitro*, or partially *in vitro* and partially *in vivo*. The contacting step and introducing step may be carried out in any order. Thus, the teachings of

Cao et al. are on point and extremely relevant to the instantly claimed invention. The reference demonstrates the unpredictability of both therapeutic transplantation and the *in vivo* manipulation of endogenous precursors for therapeutic purposes.

At page 8 of the response, with regard to Mehler et al. (1999), Applicants reiterate their earlier assertion that the issues with respect to environmental cues for differentiation of neural progenitor cells that may or may not be present in normal or neuropathological conditions are not relevant to the claimed methods reciting specific steps for differentiating cells *in vitro* or *in vivo*. Applicants reiterate that they maintain that the claims do recite specific steps for differentiating cells, noting that the claims recite the steps of contacting the progenitor cells with a differentiating agent; and introducing into the progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof, thereby differentiating the progenitor cells to produce a cell population containing neuronal cells protected from apoptotic cell death. In response, it is maintained that, with the exception of Claims 18, 19, 76, and 77, the claims do not recite specific steps for differentiating cells as Applicants continue to contend, but instead recite "contacting said progenitor cells with a differentiating agent." When the claims are given their broadest reasonable interpretation, the differentiating agent can be the *in vivo* environment of the brain, for example. The specification explicitly states that

> "Where cells are transplanted prior to differentiation, the neuronal environment can drive the cells into the desired neuronal cell type, rather than, for example, muscle cells due to the presence of the appropriate environmental cues. In view of the above, it is clear that differentiation can occur *in vitro* or *in vivo*, or can occur partially *in vitro* and partially *in vivo*." (page 59, lines 4-11)

Thus, it cannot be said that the issues with respect to environmental cues for differentiation of progenitor cells are not relevant to the claimed methods when the specification itself emphasizes the relevance of the "appropriate environmental cues."

At page 8 of the response, Applicants assert that the issues discussed in the Office Action regarding Jackowski (1995), Grados-Munro et al. (2003), and Filbin (2003) are not relevant to the

claimed methods. Applicants reiterate the language of Claim 1, but provide no support for the assertion that the references are not relevant.

At page 9 of the response, Applicants assert that they maintain that Cheng et al. (1998) provides corroborative evidence that one skilled in the art would have been able to introduce a nucleic acid molecule into human progenitor cells. Applicants reiterate that "the optimized retroviral gene-transfer protocol described by Cheng et al. is relevant to *in vivo* uses since such viral vectors are routinely used for *in vivo* transduction." Applicants further maintain that Hanazono et al. (2001) supports Applicants contention that viral vectors were routinely used for gene transfer into hematopoietic stem cells. In response, it is maintained that this contention is not accurate. Hanazono et al. states that "[t]hese vectors are being examined *in vivo* in nonhuman primate models" (page 16, column 2, paragraph 1) and acknowledges that gene transfer into human hematopoietic stem cells was problematic. The Examiner does not find that Hanazono et al. acknowledge that such vectors are routinely used for *in vivo* gene transfer into hematopoietic stem cells. Protocols for using retroviral vector to transfect human progenitor cells or human hematopoietic stem cells *in vivo* was not taught by Cheng et al. The instant claims encompass *in vivo* transduction of human hematopoietic stem cells, in the context of therapeutic protocols. As late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the claimed priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date for patentability.

At page 9 of the response, with regard to Zwaka and Thomson (2003), Applicants allege that the reference corroborates Applicants' position that electroporation can be used to produce stably transfected human ES cells. Applicants contend that the specification need not disclose, and preferably omits, this which is well known to those skilled in the art. However, given that the state of the art in June 2000 was such that no one had successfully transfected human ES cells, it cannot be said that methods for

transfecting human ES cells was well known in the art. Furthermore, the guidance provided in the specification is in the form of general guidance rather than specific guidance. When methods for the genetic modification of human embryonic stem cells are not known in the prior art, specific guidance is needed to enable the invention. However, the instant specification provides no specific guidance with regard to the genetic modification of human ES cells. Zwaka et al. (2003) was first cited by the Examiner in the rejection of record in the Office Action of 11/28/03 for documenting the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. is a post-filing reference that describes an improved electroporation method that was specially adapted for human ES cells and the instant specification does not provide specific guidance for using electroporation techniques for transfecting human ES cells. With regard to embryonic stem cells in general, the specification provides only a laundry list of techniques that could be used to introduce a nucleic acid molecule into an embryonic stem cell. With regard to human ES cells specifically, no specific guidance for their genetic modification is provided.

At page 10 of the response, Applicants assert that Eiges et al. (2001) corroborates Applicants' position that electroporation can be used to transfect human ES cells. Applicants further note that Eiges et al. describes the successful transfection of human ES cells using electroporation and two commercially available transfection reagents, Fugene and ExGen 500. Applicants further assert that Ferrari et al. (1997) and Uyttersprot et al. (1998) demonstrate that transfection methods using Fugene and ExGen 500 were available to those skilled in the art at the time of filing the priority application on June 5, 2000. Eiges et al. (2001) was first cited by the Examiner in the rejection of record in the Office Action of 11/28/03 for comparing the efficiency of several different transfection protocols for human ES cells. Eiges et al. is a post-filing reference that demonstrates the use of the transfection protocol of ExGen 500 to transfect human ES cells. However, the instant specification does not provide specific guidance for transfecting human ES cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. The teachings of Eiges et al. (2001) would not have been available to the skilled artisan as of

the claimed priority date of this application which is June 5, 2000. Applicants further assert that it would have been routine for one skilled in the art to try various known transfection methods to successfully transfect human ES cells. However, when take as a whole, in combination with the limited guidance of the specification and other unpredictabilities in the art, the lack of a known and available transfection method for human ES cells is clearly an additional obstacle that must be overcome to enable the claimed invention which is very broad in terms of the types of progenitor cells and stem cells that can be used in carrying out the claimed method. The instant specification provides no specific guidance with regard to the genetic modification of human ES cells and does not mention either FUGENE or ExGen 500 transfection reagents as being particularly suitable for the genetic modification of human ES cells. Ferrari et al. (1997) and Uyttersprot et al. (1998) likewise do not suggest using FUGENE or ExGen 500 for the genetic modification of human ES cells. Ferrari et al. teaches the transfection of lung epithelial cells by a chemical transfection method that uses ExGen 500. Uyttersprot et al. teaches the transfection of dog and human thyrocytes by a chemical transfection method that uses the transfection reagent FUGENE. Thus, at time of filing the priority application, neither the specification nor the prior art disclosed a method for the genetic modification of human ES cells and the specification did not provide specific guidance with regard to the genetic modification of human ES cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. This is a factor that must be taken into consideration when evaluating enablement across the full scope of the claims. When considered in combination with the other factors discussed in the rejection of record, the conclusion is that undue experimentation would have been required to practice the claimed invention across the full scope.

At page 10 of the response, Applicants note that the Examiner has referred to Example 6 in the prior Office Action as pertaining to adenoviral transduction when it actually pertains to the effects of the inhibition of MEF2 function. The Examiner regrets the error and appreciates Applicants clarification. The comments regarding Example 6 are hereby withdrawn.

At page 11 of the response, Applicants reiterate their comments concerning the efficiency of transfection of progenitor cells. Applicants reiterate that antibiotic selection can be used *in vitro* to select transfected progenitor cells and therefore a high efficiency of transfection of human or other progenitor cells is not needed. Applicants maintain that cell populations stably expressing an introduced nucleic acid can be routinely prepared using standard method such as antibiotic selection in order to select for a transfected population of cells. Applicants conclude that the skilled person understands that, even if progenitor cells were not transfected with particularly high efficiency, one skilled in the art would have been able to produce a population of progenitor cells predominantly or uniformly containing a MEF2 polypeptide using only routine methods. With the exception of human ES cells and human hematopoietic stem cells, the Examiner acknowledges that, when the claimed method is being carried out *in vitro*, one skilled in the art could use antibiotic selection techniques to obtain a population of progenitor cells expressing MEF2. Nevertheless, when transfection efficiencies are low, the number of cells obtained upon selection with antibiotic will also be low. Given that the specification makes it clear that the protected neuronal cells are being produced for use in transplantation protocols to treat a variety of diseases, it is not evident that low cell numbers would be sufficient to treat even a single patient. The primary problem in many transplantation protocols is to obtain a sample containing a sufficient number of neurons to treat a patient. It is therefore not evident, as Applicants continue to argue, that low transfection efficiencies would be sufficient, even with antibiotic selection to remove non-transfected cells, to produce cell populations suitable for therapeutic transplantation, the only disclosed utility for the protected neuronal cells. Obviously the same problem pertains to *in vivo* transfection protocols, which the claims also cover. If the transfection protocol is not capable of transfecting a sufficient number of cells to produce a therapeutic effect, then low transfection efficiencies would not be considered enough to enable the claimed invention over the full scope. In the instant case, neither the prior art nor the instant specification teaches the number of cells that would be needed to produce a therapeutic effect for any of

the diseases mentioned in the specification. This is an additional unpredictability that, in combination with the other factors discussed in the rejection of record, leads to a conclusion that undue experimentation would be required to practice the claimed invention over the full scope.

At page 11 of the response, Applicants assert that Milward et al. corroborates that differentiation can occur *in vivo* in injury and disease. As an example, Applicants point to Milward et al. as exemplifying an "ongoing pathological process" as distinct from "an injury model." Contrary to this contention, the myelin deficiency in the myelin-deficient rat model of Milward et al. is not the result of an ongoing pathological process, but is the result of a genetic defect which prevents the formation of myelin during **development**. There is no ongoing pathological process that attacks the myelin as it is formed. Furthermore, this model system only demonstrates the differentiation of neural stem cells to **oligodendrocytes** in the *in vivo* environment. It does not demonstrate the differentiation of progenitor cells to **neurons** in the *in vivo* environment, as instantly claimed. Nevertheless, there is no suggestion that differentiation of progenitor cells to neurons can never occur in the *in vivo* disease environment of any and all neurodegenerative diseases. The issue is whether the instant specification, in combination with the prior art, provides sufficient specific guidance to enable one of skill in the art to carry out the claimed method in all disease environments, using any type of progenitor cell and any type of differentiating agent. Here, it does not. The claims cover *in vivo* differentiation of any and all types of progenitor cells and stem cells in any and all *in vivo* disease environments, including disease environments where an ongoing pathological process is occurring. The art of record demonstrates the unpredictability and the inhibitory processes that prevent axonal growth cones from extending to appropriate partners in both the *in vivo* disease environment and healthy environment. Cell survival is also an issue in the disease environment, particularly in those where an ongoing pathological process is continuing to attack neurons and differentiating progenitor cells in the local region.

At page 12 of the response, Applicants refer to the Rule 132 Declaration of Dr. Stuart Lipton submitted on 7/19/07 as describing experimental results showing that transplanted MEF2CA neural stem cells survive, migrate and differentiate into neurons in the ischemic mouse cerebral cortex. The Declaration has been fully considered but is not found to be persuasive for the following reasons. While it is accepted that the transplanted MEF2CA-ES-derived neural stem cells survive, migrate and differentiate into neurons in the ischemic mouse cerebral cortex the cell preparation steps were carried out entirely *in vitro* and therefore it is not accepted that the experiments of the Declaration demonstrate enablement of *in vivo* embodiments, were the method steps are carried out entirely or partially *in vivo*. As to in *vivo* embodiments, the specification does not provide examples of *in vivo* differentiation or *in vivo* transfection of progenitor cells. Likewise, the instant Declaration does not address *in vivo* differentiation or *in vivo* transfection of progenitor cells appropriate to therapeutic protocols, the only utility for the *in vivo* applications. The specification provides no utility for *in vivo* applications of the claimed method in the absence of a treatment effect. The experiments described in the Declaration only pertain to the scope of the claims already acknowledged as being enabled, i.e. where the method steps are carried out entirely *in vitro* and the progenitor cells are mouse embryonic stem cells. Accordingly, the Declaration does not address the rejected scope of the claims and therefore it is maintained that claims limited to

a method of differentiating progenitor cells *in vitro*, comprising the steps of (a) contacting *in vitro* said progenitor cells with retinoic acid; and (b) introducing *in vitro* into said progenitor cells a nucleic acid molecule encoding an MEF2C polypeptide, wherein said progenitor cell is selected from the group consisting of a P19 cell and a mouse embryonic stem cell, thereby differentiating said progenitor cells to produce a cell population containing neuronal cells protected from apoptotic cell death,

would be appropriate.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20 and 78 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 78 remain indefinite in their recitation of "said population containing protected neuronal cells." Claim 1 and Claim 59 have been amended to now recite "a cell population containing neuronal cells protected from apoptotic cell death" and thus the phrase "said population containing protected neuronal cells" now lacks antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 18, 58-62, 76, and 79 stand rejected under 35 U.S.C. 102(a) as being anticipated by Okamoto et al. (2000, Proc. Natl. Acad. Sci. 97(13): 7561-7566, published online June 13, 2000).

The claims are directed to a method of differentiating progenitor cells by (a) contacting said progenitor cells with a differentiating agent, and (b) introducing into said progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof, thereby differentiating said progenitor cells to produce a cell population containing protected neuronal cells.

Okamoto et al. (2000) discloses P19 cells treated with retinoic acid and subsequently transfected with a plasmid encoding a constitutively active form of MEF2C (page 7563, column 1, paragraph 2). The reference further discloses that transfection of P19 cells with an expression vector encoding a dominant

negative form of p38α resulted in enhanced apoptotic cell death in differentiating cells (page 7565, column 2, paragraph 2). Coexpression of constitutively active MEF2C rescued the differentiating cells from apoptosis (Figure 5B and page 7565, column 2, paragraph 2). The authors conclude that the p38α/MEF2 cascade plays a role in preventing apoptotic cell death during neuronal differentiation. The neurons expressing constitutively active MEF2 represent a population of protected neuronal cells, as presently claimed.

Thus, the claimed invention is disclosed in the prior art.

At page 13 of the response, Applicants point out that Okamoto et al. was published online on June 13, 2000 and that the priority application was filed June 5, 2000. Accordingly, Applicants allege that the priority date of the subject application is prior to the publication date of Okamoto et al. The Examiner has already acknowledged that the publication date of Okamoto et al. is June 13, 2000. See the Office Action of 1/19/07 at page 20. However, the present claims are not entitled to the priority date of June 5, 2000 for the reasons of record and reasons discussed above with regard to priority. The present application fails to provide an enabling disclosure for the present claims for reasons of record and reasons further discussed hereinabove. Likewise, the priority application fails to provide an enabling disclosure. Accordingly, the Okamoto et al. is properly applied under 35 U.S.C. 102(a) and the rejection stands or falls with the enablement rejection.

Claims 1, 2, 18, 58-60, 76, and 79 stand rejected under 35 U.S.C. 102(b) as being anticipated by Krainc et al. (1998, J. Biol. Chem. 273(40): 26218-26224).

The claims are directed to a method of differentiating progenitor cells by (a) contacting said progenitor cells with a differentiating agent, and (b) introducing into said progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof, thereby differentiating said progenitor cells to produce a cell population containing protected neuronal cells.

Krainc et al. (1998) disclose that the plasmid pG/DN, containing theN-terminal DNA binding domain of MEF2C, was stably transfected into P19 cells (Figure 5 and page 26222, column 2, paragraph 2). The reference notes that these cells differentiate into a neuronal phenotype after treatment with retinoic acid, and then express MEF2C (page 26222, column 2, paragraph 2).

Thus, the claimed invention is disclosed in the prior art.

At page 14 of the response, Applicants allege that Krainc et al. provides no teaching that introducing a MEF2 polypeptide or active fragment thereof will produce a cell population containing neuronal cells protected from apoptotic cell death. First, Krainc et al. clearly teaches "introducing into said progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof" as instantly claimed. With regard to the functional language of "producing a cell population containing neuronal cells protected from apoptotic cell death," Applicants are reminded that it is well established that when the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See MPEP 2112.01 and *In re Best,* 195 USPQ 430, 433 (CCPA 1997). Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10

USPQ2d 1922, 1923 (BPAI 1989). In the instant case, there is no evidence demonstrating that the MEF2-transfected cells of Krainc et al. are functionally different from those recited in the claims. The neurons were produced using the same method as that claimed.

Claims 1, 2, 18, 58-60, 76, and 79 stand rejected under 35 U.S.C. 102(b) as being anticipated by Skerjanc et al. (4/21/2000, FEBS Letters 472(1): 53-63), as evidenced by Skerjanc et al. (1998, J. Biol. Chem. 273(52):34904-34910).

The claims are directed to a method of differentiating progenitor cells by (a) contacting said progenitor cells with a differentiating agent, and (b) introducing into said progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof, thereby differentiating said progenitor cells to produce a cell population containing protected neuronal cells.

Skerjanc et al. (2000) disclose that mouse P19 cell lines overexpressing MEF2C differentiated into neural cells in the presence of DMSO (abstract; page 54, column 2, paragraph 2; and Figure 2). At page 53, column 2, paragraph 3, the reference discloses that P19 cells overexpressing MEF2C, termed P19[MEF2C] cells, were described previously by Skerjanc et al. (1998). The 1998 reference discloses that stable cell lines expressing MEF2C were isolated upon transfection of P19 cells with 6.5 μg of a plasmid containing the *pgk-1* promoter and the coding sequence of human MEF2C, designated PGK-MEF2C (page 34905, column 1, paragraph 5). Thus, the P19 cell line was stably transfected with the MEF2C gene. The 2000 reference discloses that MEF2C can induce neurogenesis when overexpressed in P19 cells (page 53, column 1, paragraph 2 and abstract) and that neurons were observed in P19[MEF2C] cultures when aggregated with DMSO and that the neurons appeared to have a similar morphology when compared to neurons induced by retinoic acid (page 54, column 2, paragraph 1).

Thus, the claimed invention is disclosed in the prior art.

At page 15 of the response, Applicants object to the Examiner's assertion in the Office Action of 1/19/07 that Skerjanc et al. (2000) "discloses that MEF2C can induce neurogenesis when overexpressed in P19 cells." Nevertheless, the teachings of the reference art explicit. The abstract states

> MEF2C is a transcription factor expressed in neural lineages. After transient transfection, the MEF2 family of factors can act synergistically with the neural-specific transcription factor, MASH-1, and activate exogenous neural-specific promoters. To determine whether MEF2C is capable of modulating endogenous gene expression, P19 cell lines were analyzed that overexpressed MEF2C, termed p19[MEF2C] cells. Here we show that P19[MEF2C] cells differentiate into neurons when aggregated with ME_2SO. MEF2C-induced neurons expressed neurofilament protein, the nuclear antigen NeuN, as well as MASH-1. **Our results indicate that MEF2C can directly or indirectly activate the expression of MASH-1, leading to neurogenesis.** (abstract, emphasis added).

Likewise, the reference further explicitly states "[h]ere we show that MEF2C can induce neurogenesis when overexpressed in P19 cells" (page 53, column 2, paragraph 2, last sentence). The explicit teachings of the reference cannot be refuted. Thus, it is maintained that Skerjanc et al. (2000) discloses that MEF2C can induce neurogenesis when overexpressed in P19 cells.

At page 15 of the response, Applicants cite Skerjanc et al. (2000) at page 54, left column, where it says "P19 cells differentiate into neuroectodermal lineages when aggregated with retinoic acid but not when aggregated with ME_2SO or in the absence of retinoic acid." Applicants conclude by saying "[t]hus, DMSO does not cause P19 cells to differentiate into neuroectodermal lineages, in contrast to retinoic acid." However, the cited statement of Skerjanc et al. clearly refers to non-transfected P19 cells. Reading a little further into the next sentence, one finds that the properties of non-transfected P19 cells are contrasted with the properties of P19[MEF2C] cells. Skerjanc states

> "[t]o examine whether MEF2C can activate the expression of endogenous genes in the neuronal pathway, P19[MEF2C] cells were aggregated in the presence and absence of ME_2SO. Immunofluorescence was performed with an anti-neurofilament antibody, MF68 [17,23], and with an anti-NeuN antibody [27]. **Neurons were observed in P19[MEF2C] cultures that were aggregated with ME_2SO**, as shown by the expression of neurofilament protein (Fig. 1B) and by the nuclear expression of NeuN (Fig. 1D). **As expected, control P19 cells did not express neuron-specific proteins when aggregated with ME_2SO** (Fig. 1A,C). The neurons appeared to have similar morphology when

> compared to neurons induced by retinoic acid [17]." (page 54, paragraph bridging columns 1-2; emphasis added).

Despite the teaching that non-transfected P19 cells do not differentiate into neuroectodermal lineages when aggregated with DMSO, this is of no relevance because the present claims do not require the use of DMSO to differentiate wild-type P19 cells. The present claims read on the use of any differentiating agent, including particularly retinoic acid, wherein the differentiating agent is contacted to any type of progenitor cell. Skerjanc et al. (2000) clearly teach the use of several differentiating agents, including retinoic acid, as set forth in the rejection of record.

At page 16 of the response, Applicants allege that Skerjanc et al. (2000) "provides no teaching of introducing into progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof." Not true. Skerjanc et al. (2000) explicitly states that "the isolation of P19 cells overexpressing MEF2C, termed P19[MEF2C] cells, have been described previously [24]." Reference 24 is Skerjanc et al. (1998) cited in the rejection of record. Not only does the 1998 reference disclose "introducing into progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide" as set forth in the present claims, it also discloses that stable cell lines expressing MEF2C were isolated upon transfection of P19 cells with 6.5 μg of a plasmid containing the *pgk-1* promoter and the coding sequence of human MEF2C, designated PGK-MEF2C (page 34905, column 1, paragraph 5). Thus, the P19 cell line was stably transfected with the MEF2C gene.

At page 16 of the response, Applicants allege that Skerjanc et al. (2000) provides no teaching that introducing a MEF2 polypeptide or active fragment thereof will produce a cell population containing neuronal cells protected from apoptotic cell death. However, with regard to the functional language of "producing a cell population containing neuronal cells protected from apoptotic cell death," Applicants are reminded that it is well established that when the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See MPEP 2112.01 and *In re Best,* 195 USPQ 430, 433 (CCPA 1997). Where the claimed and prior art products are

identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). In the instant case, there is no evidence demonstrating that the neurons of Skerjanc et al., produced by the same method instantly claimed, are functionally different from those recited in the claims.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER